Pregnancy Outcomes and Pharmacokinetics in Pregnant Women Living With HIV Exposed to Long-Acting Cabotegravir and Rilpivirine in Clinical Trials

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Introduction

- Cabotegravir (CAB) + rilpivirine (RPV) administered monthly or every 2 months is the first complete long-acting (LA) regimen recommended in treatment guidelines[1,2] for the maintenance of HIV-1 virologic suppression.
- Data from non-clinical reproductive toxicology studies with CAB[3] and RPV[4] did not detect adverse developmental outcomes at clinically relevant exposures.
- In ViiV-sponsored clinical trials of CAB + RPV LA, pregnancy was exclusionary, and women of reproductive age were required to use highly effective methods of contraception.
- Therefore, limited data[5,6] exist among women living with HIV becoming pregnant while exposed to CAB + RPV LA in ViiV-sponsored clinical trials.
  - CAB LA and RPV LA pharmacokinetic (PK) tails in 3 pregnant women with subsequent live births were within the range of non-pregnant women during pregnancy and post-partum.[5,6]
- In this update, we report pregnancy outcomes in additional women exposed to CAB + RPV along with PK tail data during pregnancy and post-partum among those with live births who received CAB + RPV LA.

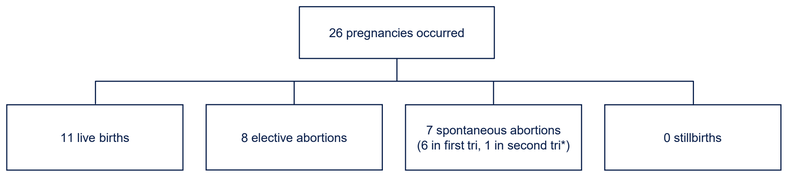
Methods

- Data in women who were exposed to ≥1 dose of CAB + RPV (oral/LA) and became pregnant in ViiV-sponsored Phase 2/3/3b[7–10] clinical studies through program inception and within the compassionate use program were included in the analysis.
- Per protocol, CAB + RPV was discontinued following identification of pregnancy and an alternative antiretroviral therapy (ART) regimen initiated, with continued quarterly CAB and RPV PK sampling for 52 weeks post last injection in the long-term safety follow-up (LTFU).
- Descriptive characteristics of pregnant women were summarized, including formulation and duration of CAB + RPV (oral/LA) treatment prior to conception, relevant past obstetric history, and birth outcomes.
- Available CAB and RPV LA PK profiles during pregnancy and post-partum in women with live births were graphically represented.

Results

- Through March 31, 2021, 23 pregnancies were reported by 21 women among 325 clinical trial participants exposed to CAB + RPV, with an additional 3 pregnancies reported by 2 women in the compassionate use program (**Figure 1**).
  - 5 pregnancies with oral CAB + RPV exposure only.
  - 21 pregnancies with CAB + RPV LA exposure (including 4 during PK tail after previously stopping LA treatment).
- There were 11 live births, 1 following oral and 10 following LA exposure (**Table 1**).
  - 1 live birth of a pre-term infant had reported congenital ptosis.
- A total of 8 elective abortions (all in first trimester of gestation) were reported (**Table 2**).

Figure 1. Summary of Pregnancy Outcomes With CAB + RPV Exposure



*Reported by investigator as spontaneous abortion at 23 weeks GA with IUGR in a mother with multiple risk factors. Total rate of miscarriage is similar to that reported in other clinical trials.[11]
CAB, cabotegravir; IUGR, intrauterine growth restriction; RPV, rilpivirine; tri, trimester.

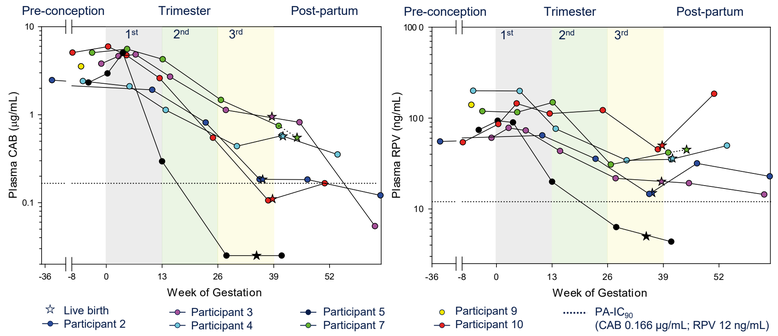
Table 1. Summary of Live Birth Outcomes Following CAB + RPV Exposure

Participant #	CAB + RPV dosing regimen	Duration of exposure prior to conception*	Alternative oral ART during pregnancy	Pregnancy outcome
1	Oral (daily)	<1 week	RAL+TAF/FTC	Term, normal birth weight, no congenital anomaly
2	Q8W	87 weeks	RAL+TDF+3TC	Term, normal birth weight, no congenital anomaly
3	Q4W	35 weeks	DRV/r+TDF/FTC	Term, normal birth weight, no congenital anomaly
4	Q4W	204 weeks	DTG/ABC/3TC	Term, normal birth weight, no congenital anomaly
5	Q4W	37 weeks	EFV/TDF/FTC	Term, birth weight undocumented, no congenital anomaly
6	Q4W	81 weeks	DRV/r+TDF/FTC	Term, normal birth weight, no congenital anomaly
7	Q4W	106 weeks	RAL+TDF/FTC	Term, normal birth weight, no congenital anomaly
8†	Q4W	38 weeks	Continued LA dosing	Term, low birth weight, congenital ptosis (IUGR; multiple maternal risk factors)
9	Q4W (PK tail‡)	Last injection 10 weeks prior to conception	DTG/ABC/3TC	Term, normal birth weight, no congenital anomaly
10	Q4W	36 weeks	RPV/TDF/FTC	Term, normal birth weight, no congenital anomaly
11	Q4W (PK tail‡)	Last injection 28 weeks prior to conception	DTG/RPV; RPV/TDF/FTC	Pre-term (36 weeks GA), normal birth weight, no congenital anomaly

*Conception was estimated to be 14 days following documented LMP. Duration of prior LA exposure includes ≥4 weeks of oral CAB + RPV OLI dosing prior to CAB + RPV LA. †2nd pregnancy, 1st pregnancy corresponds to participant 11 in Table 2. ‡Pregnancy detected during PK tail after CAB + RPV LA discontinued. 3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; CAB, cabotegravir; DTG, dolutegravir; DRV/r, darunavir/ritonavir; EFV; efavirenz; FTC, emtricitabine; GA, gestational age; IUGR, intrauterine growth restriction; LA, long-acting; LMP, last menstrual period; OLI, oral lead-in; PK, pharmacokinetic; Q4W, every 4 weeks; Q8W, every 8 weeks; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.

- All 10 women exposed to CAB + RPV LA and 1 woman exposed to oral CAB + RPV with subsequent live birth outcomes remained virologically suppressed from conception through pregnancy and post-partum or last available viral load assessment following switch to alternative ART or during continued LA dosing.
- Plasma CAB and RPV concentrations were available for 7/10 women exposed to LA therapy with live birth outcomes (**Figure 2**).

Figure 2. Maternal CAB and RPV PK Tails Following CAB + RPV LA Discontinuation Throughout Pregnancy and Post-Partum



- CAB and/or RPV concentrations in the tail may have been impacted by metabolic induction or the inhibition propensity of the subsequent alternative ART regimen participants were switched to after LA discontinuation.*
- Among women discontinuing CAB + RPV LA due to pregnancy, plasma CAB and RPV concentrations during pregnancy were within the range of concentrations observed in non-pregnant women.

*PK tail concentrations may have been affected for the following participants: participant 3, RPV PK by inhibition through DRV/r; participant 5, CAB + RPV PK by induction from EFV; participant 10, RPV PK by taking oral RPV after stopping RPV LA. CAB, cabotegravir; DRV/r, darunavir/ritonavir; LA, long-acting; PK, pharmacokinetic; PA-IC_{90}, protein binding–adjusted 90% inhibitory concentration; RPV, rilpivirine.

Table 2. Summary of Non-Live Birth Outcomes Following CAB + RPV Exposure

Participant #	CAB + RPV dosing regimen	Duration of exposure prior to conception*	Relevant past obstetric history	Pregnancy outcome
1	Oral daily	1 week	2 full-term normal births, 2 induced abortions	Spontaneous abortion (first trimester)
2	Oral daily	3 weeks	5 pre-term and 2 full-term pregnancies with 2 normal births and 3 spontaneous abortions	Spontaneous abortion (first trimester)
3	Oral daily	2 weeks	1 premature birth, 1 spontaneous abortion	Elective abortion for nausea/vomiting (first trimester)
4	Oral daily	4 weeks	2 prior children (details unknown)	Spontaneous abortion (first trimester)
5	Q4W	71 weeks	2 full-term normal births	Elective abortion (first trimester)
6	Q4W	11 weeks	1 full-term normal birth, 3 pre-term births, 1 still-birth, 2 induced abortions	Elective abortion (first trimester)
7	Q4W	12 weeks	2 full-term normal births, 1 elective abortion	Elective abortion (first trimester)
8	Q4W	110 weeks	2 full-term normal births, 2 elective abortions	Spontaneous abortion (first trimester)
9	Q4W	57 weeks	No previous pregnancies	Spontaneous abortion (first trimester)
10	Q4W	189 weeks	1 elective abortion	Spontaneous abortion (first trimester)
11	Q4W + oral ART†	3 weeks	No previous pregnancies	Spontaneous abortion at 23 weeks GA, IUGR. Multiple maternal risk factors
12	Q8W	195 weeks	2 full-term births	Laparotomy for ectopic pregnancy (first trimester)‡
13	Q8W	92 weeks	1 full-term normal birth	Elective abortion (first trimester)
14[5]	Q8W (PK tail‖)	Last injection 38 weeks prior to conception	1 full-term normal birth, 1 elective abortion	Elective abortion (first trimester)
15¶	Q4W (PK tail‖)	Last injection 54 weeks prior to conception	1 full-term normal birth	Elective abortion (first trimester)

*Conception was estimated to be 14 days following documented LMP. Duration of prior LA exposure includes ≥4 weeks of oral CAB + RPV OLI dosing prior to CAB + RPV LA. †Cobicistat/darunavir/emtricitabine/tenofovir alafenamide. ‡Classified in medical database as elective abortion. §2nd pregnancy, 1st pregnancy corresponds to participant 13 in Table 2. ‖Pregnancy detected during PK tail after CAB + RPV LA discontinued. ¶2nd pregnancy, 1st pregnancy corresponds to participant 3 in Table 1. ART, antiretroviral therapy; CAB, cabotegravir; GA, gestational age; IUGR, intrauterine growth restriction; LA, long-acting; LMP, last menstrual period; OLI, oral lead-in; PK, pharmacokinetic; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

Conclusions

- Pregnancy outcomes in women exposed to CAB + RPV (oral/LA) at conception are consistent with earlier findings.[5,6]
- There was 1 reported congenital anomaly (congenital ptosis) among 11 live births.
- The CAB LA and RPV LA PK tails in pregnancy were within the observed range for non-pregnant women, taking into account the alternative antiretroviral regimen they switched to.
- Ongoing monitoring of birth defects within the Antiretroviral Pregnancy Registry and pregnancy surveillance within the clinical program continues.

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